Case Study / Discussion

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Scenario

- Drug "X": NCE / anti-epileptic
- No significant pre-clinical issues
- Phase I (6 studies)
  - significant PK variability
  - marked AEs of rash and / or cough (n=14/72)
- Phase II (initial POC study)
  - significant PK variability noted again
  - similar AE profile & incidence (n=8/35)

Metabolism Information

- Preclinical *in vitro* studies show that Drug X is metabolized predominately by
  - CYP3A4 and CYP3A5 (accounts for >70%)
  - and to a lesser extent by CYP2C19 (<30%)
- *In vitro* data suggests that Drug X interacts with transporter genes ABCB1 and potentially ABCG2
- Note: CYP2C19 is a "known valid biomarker"

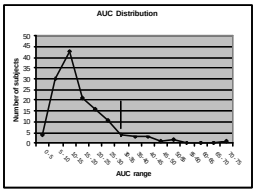
Inter-individual variation of Drug X plasma concentrations

Inter-individual variation of Drug X plasma concentrations has been consistently observed in both Phase I & Phase II

- AUC range 1.43 - 73.23 ng.hr/ml
- Cmax range 0.258 - 4.511 ng/ml
- Tmax range 0.75 – 12 hours
- 10-20% incidence of "outliers" with marked PK variability
- Note: Not all subjects with marked PK variability had rash and/or cough (AE incidence approx. 20%)

Pharmacogenetics and PK / AE - analyses

- Evaluation (retrospective) of Drug X examining association of pharmacokinetic (PK) variability, rash and cough (18 subjects with defined moderate/severe AEs)
- Combined Ph I & Ph II studies (7 in total) to increase power
- Five candidate genes known to play a role in metabolism of Drug X: CYP2C19, CYP3A4, CYP3A5 and ABCB1, ABCG2
- Subjects: 107 subjects in total - 72 healthy volunteers from six phase I studies and 35 patients from a Ph II study



Subject/Phenotype Breakdown

Phenotype	# of 'phenotypic events' (ph I / Ph II)	# of 'controls'
AUC	13 (9/4)	87
Cmax	10 (7/3)	90
Tmax	19 (13/6)	81
Cough	18 (11/7)	89
Rash	15 (10/5)	92

Analyses Conducted Retrospectively after Ph I studies and initial Ph II (7 studies combined)

- Single-point (genotypic and allelic) association analyses of SNPs
- Hardy-Weinberg analysis to confirm genetic segregation
- Linkage disequilibrium (LD) analyses

CYP2C19

- 22 SNPs within the CYP2C19 gene showed association ($p<0.01$) with incidence of **rash** and 6 of these SNPs showed association ($p<0.01$) with incidence of **cough**
- CYP2C19 *2/*2 genotypic p -value was p=0.001 for cough and p=0.0016 for **rash**
- LD in CYP2C19 was generally low; not all of the SNPs associated with rash and cough were in strong LD
- Additionally, 13 different SNPs in CYP2C19 showed association with **Tmax** ($p<0.01$)

ABCB1

- 16 SNPs in the ABCB1 gene showed single-point association with **Tmax** ($p<0.01$) in Caucasians
- the 16 SNPs noted above were not in strong LD
- 4 SNPs in ABCB1 showed association with AUC and Cmax

Summary of Significant Results

- Association was observed between SNPs in CYP2C19 with **rash**, **cough** and **Tmax**
- Association was observed between SNPs in ABCB1 with **Tmax**
- No evidence for association was observed in ABCG2, CYP3A4 or CYP3A5
- 3 of 3 subjects homozygous for CYP2C19*2 had rash and cough

DISCUSSION

AUDIENCE AND PANEL PARTICIPATION

Firstly, let's consider what might be done differently vs what the Sponsor did:

(i) Prior to going into FTIH, would you have planned to proactively genotype in Phase I?

1. No
2. Yes (CYP3A4, CYP3A5, CYP2C19, ABCB1, ABCG2)
3. CYP3A4, CYP3A5 and CYP2C19 only
4. A more comprehensive DME panel

(ii) Following review of the phenotypic (PK & AE) data from the 6 completed Phase I studies, would you have retrospectively genotyped samples from those studies at that point?

1. No
2. Yes (CYP3A4, CYP3A5, CYP2C19, ABCB1, ABCG2)
3. CYP3A4, CYP3A5 and CYP2C19 only
4. A more comprehensive DME panel

(iii) Would your response to the previous question be affected if the major metabolic pathway was via a "known valid biomarker"?

1. Yes
2. No

(iv) Following review of the phenotypic (PK & AE) data from the 6 completed Ph I studies, would you have planned to proactively genotype samples from the next Phase II POC study?

1. No
2. Yes (CYP3A4, CYP3A5, CYP2C19, ABCB1, ABCG2)
3. CYP3A4, CYP3A5 and CYP2C19 only
4. A more comprehensive DME panel

(v) Would your response to the previous question be affected if the major metabolic pathway was via a "known valid biomarker"?

1. Yes
2. No

Now let's turn to the results that the Sponsor actually obtained:

(vi) Would you prospectively plan to replicate the findings / confirm the data (e.g. in a follow up Ph II study)?

1. Yes
2. No

(vii) If the initial data are confirmed / replicated, would you prospectively stratify in a subsequent study for dosing (e.g. Ph III)?

1. Yes
2. No

(viii) If the initial data are confirmed/replicated, do you consider that the genetic association data sufficiently demonstrate a correlation between PK variability and the SNPs analysed such that continued evaluations be carried out?

1. Yes
2. No

(ix) If the initial data are confirmed/replicated, do you consider that the genetic association data sufficiently demonstrate a correlation between AEs and the SNPs analysed such that continued evaluations be carried out?

1. Yes
2. No

(x) If the initial data are confirmed/replicated, do you consider that this may constitute the basis for pursuing development of Drug X with a diagnostic test for potential prediction of optimal dosing?

1. Yes
2. No

(xi) If the initial data are confirmed/replicated, do you consider that this may constitute the basis for pursuing development of Drug X with a diagnostic test for potential prediction of AEs (rash, cough)?

1. Yes
2. No

(xii) If the initial data are confirmed/replicated, do you consider that these data may have implications for identifying those patients most likely to show efficacy?

1. Yes
2. No

Acknowledgements